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10/562,059	12/22/2005	Yasuhiro Kajihara	TAM-058	9645

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EXAMINER	
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ART UNIT	PAPER NUMBER
1623	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/562,059	KAJIHARA ET AL.	
	Examiner	Art Unit	
	Eric S. Olson	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 December 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *December 22, 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12/25/2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Detailed Action

This application is a national stage application of PCT/JP04/09521, filed June 29, 2004, which claims priority to foreign application JP2003-187931, filed June 30, 2003. Claims 1-20 are pending in this application and examined on the merits herein. Applicant's preliminary amendment submitted December 22, 2005 is acknowledged wherein claims 5, 9, and 10 are amended, new claims 11-20 are introduced, and the specification is amended to more clearly state the name of the compound disialoundecaoligosaccharide.

Claim Objections

Claims 17-20 are objected to because of the following informalities: Claim 17 recites the grammatically incorrect phrase "curing virus diseases." The correct phrase is probably, "curing **viral** diseases." Claims 18-20 recite, "curing influenza virus infectious diseases." The grammatically correct statement is, "curing influenza **viral infections**." Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-20 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for specific asparagine-linked

disialoundecaoligosaccharide-fatty acid amides disclosed in the specification, does not reasonably provide enablement for any asparagine-linked disialoundecaoligosaccharide-fatty acid amide whatsoever. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The Applicant's attention is drawn to *In re Wands*, 8 USPQ2d 1400 (CAFC1988) at 1404 where the court set forth eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

(1) The nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

Nature of the invention: The claimed invention is a chemical compound comprising a disialo-oligosaccharide linked to asparagine linked to a fatty acid. In order for a compound to be enabled by the specification, the specification must enable one skilled in the art to use the compound for some purpose.

The state of the prior art: Certain glycoproteins can be degraded to produce asparagine-linked oligosaccharides containing sialic acid, for example Lowe et al. and Endo et al., both of which are included with Applicant's form PTO-1449. However, these compounds and their fatty acid derivatives are not known in the art to be useful for any purpose, for example as therapeutic agents.

The relative skill of those in the art: The relative skill in the art is high.

The predictability or unpredictability of the art: There exist man different sialyl-containing polysaccharides *in vivo* and many molecular receptors or other proteins that recognize them. The diversity of possible carbohydrate structures leads to a vast diversity of different biological effects. Therefore for any novel carbohydrate, it is highly unpredictable what effect it will produce *in vivo* or what possible biological or medical use, if any, it might have. Therefore the subject matter of the claimed invention is highly complex.

The Breadth of the claims: The claimed invention includes any molecule whatsoever that includes an oligosaccharide of 11 units, straight or branched, containing two sialic acid units, with the oligosaccharide linked to an asparagine molecule which is linked to a fatty acid by an amide bond. Therefore an enormous diversity of different carbohydrate structures are included in the claimed invention.

The amount of direction or guidance presented: Applicant's specification discloses that certain specific asparagine-linked disialoundecaoligosaccharide-fatty acid amides inhibit influenza sialidase, and are thus potentially useful for the treatment of influenza. This activity is not shown to be present in any significant fraction of the vast diversity of carbohydrates included within the scope of the claimed invention.

The presence or absence of working examples: no working examples are shown for any practical use of the claimed invention, for example treatment of influenza.

Note that lack of working examples is a critical factor to be considered, especially in a case involving an unpredictable and undeveloped art such as the biological role of complex oligosaccharides. See MPEP 2164.

The quantity of experimentation necessary: In order to actually use the vast majority of oligosaccharides falling within the scope of the claimed invention, one skilled in the art would have to determine what the various oligosaccharides can actually be used for. Applicant's specification only provides one possible use for a narrow group of these compounds. One skilled in the art would thus have to undertake a large-scale program of research in order to discover novel uses for many novel compounds, And to determine which of these compounds are or are not useful for anything in the first place. Doing so would involve an undue burden of unpredictable experimentation.

Genentech, 108 F.3d at 1366, sates that, "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion." And "patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable."

Therefore, in view of the Wands factors, as discussed above, particularly the breadth of the claims and the unpredictability of the art, Applicants fail to provide information sufficient to practice the claimed invention for all possible asparagine-linked disialoundecaoligosaccharide-fatty acid amides.

Claims 9, 10, and 17-20 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a drug for treating influenza virus

infection, does not reasonably provide enablement for a drug for preventing and/or curing viral infections. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The Applicant's attention is drawn to *In re Wands*, 8 USPQ2d 1400 (CAFC1988) at 1404 where the court set forth eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

(1) The nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary. "Prevention" as discussed herein is interpreted to mean the complete blocking of all symptoms or effects of a disorder for an indefinite period of time.

Nature of the invention: The claimed invention is drawn to a therapeutic method for treatment or prevention of a disorder. Merriam-Webster's Collegiate Dictionary (reference included with PTO-892) defines "prevent" as meaning, "to deprive of power or hope of acting or succeeding," or "to keep from happening or existing." This definition is taken as representing the ordinary usage of the term "preventative". In order to deprive something of power or hope of acting or succeeding, the preventative agent must be completely effective. "Prevention" as recited in the instant claims, is interpreted to mean the complete and total blocking of all symptoms of a disorder for an

indefinite period of time. Merely slowing the onset of disease or making the disease less likely would still leave it with "power or hope of acting or succeeding," and thus not qualify as prevention.

The state of the prior art: Sialidase inhibitors are known in the prior art to be useful for inhibiting the replication of influenza virus. They are not known to be useful as preventative agents in the sense being used herein. In general, prevention of any disorder in the sense being used herein is not a recognized clinical outcome in the art, as no treatment is perfectly effective.

The relative skill of those in the art: The relative skill of those in the art is high.

The predictability or unpredictability of the art: Prevention of a disease is not the same as treatment of said disease. In order to prevent a disease, as opposed to merely delaying or reducing its symptoms, a treatment must either render the subject completely resistant to said disease after a single treatment or a limited number of treatments, or else, when continued indefinitely, continue to completely suppress the occurrence of said disease. In order to practice a preventative method, one of skill in the art must know the answer to several questions in addition to the effectiveness of the therapy in short-term relief of symptoms, including:

1) What is the duration of a single course of therapy? How often must the therapy be administered to completely suppress the disease?

2) Does the subject develop tolerance to the therapy over time? Does the disease eventually progress to a point where the therapy is unable to completely suppress all symptoms? For example, will a metastatic cancer eventually adapt to

overcome treatments directed to preventing it from metastasizing into the bone? Or will a case of osteoporosis or rheumatoid arthritis ultimately progress to a point where symptoms develop regardless of which therapy is administered.

3) What are the long-term effects of the therapy? Does it cause progressive damage to the kidneys, liver, or other organs? Does the active agent accumulate in the subject's tissues? Is the minimum dose necessary to completely prevent the disease safe for long-term administration? Are there any steps that can be taken to reduce side effects?

For this reason, many therapies which are suitable for short-term relief of symptoms are not suitable for lifelong prevention of disease. For example, antivirals, antibiotics, chemotherapeutics, and antiviral drugs are not normally administered to healthy subjects in order to prevent the development of infection or cancer.

The Breadth of the claims: In the absence of an explicit definition in Applicant's specification, the claims are given their broadest reasonable interpretation. See MPEP 2111. As discussed above, the broadest reasonable interpretation for the term "prevention" requires complete efficacy in suppressing all effects of a disorder.

The amount of direction or guidance presented: No guidance is given in the specification suggesting any reason to believe that the claimed compounds are uniquely useful as preventative agents. All that is demonstrated is the ability of these compounds to inhibit the activity of influenza virus on avian cells in an *in vitro* culture.

The presence or absence of working examples: No working examples are given of any therapeutic methods whatsoever.

Note that lack of working examples is a critical factor to be considered, especially in a case involving an unpredictable and undeveloped art such as the prevention of disease. See MPEP 2164.

The quantity of experimentation necessary: As mentioned above, the short-term usefulness of a therapy for relief of symptoms is no guarantee of its long-term usefulness for prevention of disease. Because no guidance is given for the use of the claimed therapeutic method for the long-term prevention of disease, one skilled in the art wishing to practice the invention would be unable to do so without first gathering information as to the long-term effectiveness of the therapy. In particular, one skilled in the art, in order to practice the invention for prevention of disease, would need to know whether the preventative effect remains potent over the long term.

In order to answer these questions in the absence of any existing data, one skilled in the art, in order to practice the invention, would undertake long-term animal tests, preferably over a period of years, preferably involving a relatively long-lived experimental animal such as dogs or monkeys, or a human clinical trial. Animal experiments include, along with induction of the disease state, administration of the potential pharmaceutical compound and collection and analysis of data, additional burdens associated with compliance with animal welfare regulations, care, feeding, and other maintenance of the animals, dissection of dead animals to collect data, and disposal of dead animals after the protocol is finished. Administering the claimed compounds for a period of years to a suitable subject population is an undue amount of experimentation needed in order to practice the full range of the claimed invention. As

prevention in the full sense is an extremely high bar for any clinical outcome, there is no reason to believe that the therapy would be successful, and any actual success would be a surprising and unpredictable result.

Genentech, 108 F.3d at 1366, sates that, "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion." And "patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable."

Therefore, in view of the Wands factors, as discussed above, particularly the breadth of the claims and the nature of the invention, Applicants fail to provide information sufficient to practice the claimed invention for a drug for the prevention of viral infection.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-5, 7-13, and 17-20 are rejected under 35 U.S.C. 102(b) as being anticipated by Michel et al. (Reference included with PTO-892) Michel et al. discloses a coupling of sialoglycopeptides to fatty acids. (p. 2365, first paragraph of introduction, p. 2366 under the heading *Coupling Reaction*) A glycopeotide comprising a biantennary disialo-undecaoligosaccharide linked to asparagine was isolated and coupled to palmitic

acid, which is a 16-carbon straight-chain saturated fatty acid. (p. 2367, under the headings *Glycopeptide Isolation* and *Coupling*) This conjugate is an asparagine-linked disialoundecaoligosaccharide according to the instant claims, and is reasonably considered to have the utility disclosed in the instant claims for treating influenza. Furthermore, it is dissolved in DMSO, which is reasonably considered to be a pharmaceutical additive. (p. 2367, bottom of page) Therefore the claimed invention is anticipated by Michel et al.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 6 and 14-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Michel et al. (Reference included with PTO-892) in view of Remington: The Science and Practice of Pharmacy, Twentieth Edition. (Reference included with PTO-892, herein referred to as Remington) The disclosure of Michel et al. is discussed above. Michel et al. does not disclose a composition further comprising any of the additives recited in instant claims 6 and 14-16.

Remington discloses glycerin as a pharmaceutical solvent, (p. 735, left column paragraph 4) and lactose, mannitol, glucose, and sucrose as diluents or binders for pharmaceutical tablets. (p. 860, left column last paragraph, right column paragraph 4)

It would have been obvious to one of ordinary skill in the art at the time of the invention to add any of the additives disclosed by Remington to the compounds discussed by Michel et al. These additives are well known in the art, and one of ordinary skill in the art would have realized that they could be productively used as a binder, diluent, or solvent for a prior art active agent.

Thus the invention taken as a whole is *prima facie* obvious.

Conclusion

No claims are allowed in this application.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Eric S. Olson whose telephone number is 571-272-9051. The examiner can normally be reached on Monday-Friday, 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shaojia Anna Jiang can be reached on (571)272-0627. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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